Summer 8-11-2012

Denosumab Versus Bisphonoates for the Prevention of Skeletal Related Events in Patients With Solid Tumor and Multiple Myeloma

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Method: An exhaustive search of available medical literature was performed using the following databases: Medline, CINAHL, and Web of Science. A cited reference search was performed using Web of Science. The keywords used were denosumab, RANK ligand, bisphosphonates, solid tumors, and multiple myeloma.

Results: Three RCTs that met inclusion criteria were analyzed and were relevant for the purposes of this systematic review. Results are as follows: Median time, in months, to first on-study SRE in Fizazi et al, (denosumab: 20.7, zoledronic acid: 17.1; HR, 0.82), Stopeck et al (denosumab: not reached, zoledronic acid: 26.4; HR, 0.82), Henry et al (denosumab: 20.6, zoledronic acid: 16.3; HR, 0.84).

Conclusion: Denosumab has proven to be better than bisphosphonates (particularly zoledronic acid) for the prevention of skeletal related events in patients with solid tumor malignancy or multiple myeloma. Denosumab is easier to administer, can be used without dose adjustment for renal impairment or renal monitoring, and has lower incidence of renal failure and acute phase reactions. Monitoring for hypocalcemia is important, and a supplement should be given as indicated. There is not a significant difference between incidence of osteonecrosis of the jaw (ONJ), or overall survival and disease progression with either denosumab or bisphosphonates.

Keywords: Denosumab, RANK ligand, Bisphosphonates, solid tumors, multiple myeloma

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

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Keywords
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A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 11, 2012

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[Information redacted for privacy]

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Acknowledgements

To *my family*: There is no chance I would be here without you. Thank you for your unending and unconditional love, encouragement, support and faith in me. I love you each uniquely and am ever grateful for your presence in my life.

To *my fiance*: I am so grateful to have such an amazing partner in life to take this journey with me. You are my rock and my peace. I love you more than words can say.

To *my Uncle Richie and Grandma*: You are never forgotten… I love you. I miss you. And I hope to make you proud. This work and my future oncology pursuits are dedicated to you.

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List of Abbreviations

SRE……..Skeletal Related Events

ONJ…….....….Osteonecrosis of the Jaw

CI..... Confidence Interval

SQ…….subcutaneous

IV…….intravenous

HR……..…Hazard Ratio

RR……...relative risk

RCT…….Randomized Controlled Trial

Den……..Denosumab

ZA……Zoledronic Acid

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BACKGROUND

Overview of Problem

Skeletal related events (SREs) have been defined by researchers as pathological fracture, radiation or surgery to the bone, or spinal cord compression.[1-3] The frequency of SREs in women with breast cancer, as an example, was reported in a study published in 1998 as follows: hypercalcemia of malignancy 19%, pathological fracture of a long bone 19%, spinal cord compression 10%.[4] The occurrence of SREs is patients with solid tumors and multiple myeloma is a concern for both patient and provider due to the subsequent morbidity and risk for further complications. Coleman[5] sets forth the following list, which describes possible outcomes of skeletal complications: pain, impaired mobility, hypercalcemia, pathological fracture, spinal cord compression or nerve root compression, and bone marrow infiltration. These problems present their own risks and have potential to lead to additional sequelae, including known adverse effects of opioid use for pain management, risks of surgical management or radiation therapy, end-organ damage or mortality from hypercalcemia, paralysis secondary to untreated spinal cord compression, [5] and others that will not be addressed here.

Hypercalcemia- One source [6] states, "Hypercalcemia is the most common paraneoplastic endocrine syndrome, occurring in 25% of malignancies. In the great majority of patients (98%), the identity of the tumor is apparent at the time of

presentation, and the prognosis is poor, as most patients with hypercalcemia of malignancy do not survive beyond 6 months." Hypercalcemia of malignancy occurs most commonly as a result of parathyroid hormone related protein (PTHrP), in addition to other endocrine pathways of bone resorption.[6] In multiple myeloma, "Hypercalcemia and lytic bone lesions are among the diagnostic criteria…" [6] Hypercalcemia can lead to problems for the patient, among the more severe of which are renal failure and cardiac arrhythmia potentially leading to death. [5] Because bone resorption is a significant cause of hypercalcemia of malignancy,[6] this condition must be treated with the most aggressive (and least toxic) therapy available.

Pathophysiology of events associated with bone metastasis- In the text *Greenspan's Basic & Clinical Endocrinology* [6] (chapter 21 titled Humoral Manifestations of Malignancy), the author gives the following explanation of the humoral mediators associated with bone resorption in malignancy.

> When tumor expression of PTHrP results in inappropriately high levels of PTHrP that reaches bone cells through the circulation or following synthesis in the bone microenvironment, a vicious cycle can ensue. PTHrP stimulates the expression of RANKL (receptor activator of NF-κB ligand) by osteoblasts. RANKL, the primary gatekeeper modulating bone resorption in health and disease, *stimulates* osteoclast differentiation and function via binding to its receptor, RANK, on osteoclasts and their precursors. Increased numbers of activated osteoclasts are generated both by the local release of PTHrP, in the case of bone metastases, or by high levels of the hormone [calcitonin] produced by tumor cells in

extraskeletal sites. Both mechanisms cause enhanced bone resorption. In the case of bone metastases, sequestered growth factors, such as transforming growth factor (TGF)-beta, released locally from the bone matrix during resorption, further enhance tumor cell secretion of PTHrP.

This process illustrates one mechanism for the development of SREs in cancer patients. Therapeutic agents that act to inhibit the pathological process in bone, thereby decreasing the rate of SREs, are beneficial and essential to the overall management of the patient.[7]

Purpose of Study

It is well known in oncology that bisphosphonates (a class of drugs, one of which is zoledronic acid) are effective in the prevention of SREs, the treatment of bone pain associated with malignancy, as well as hypercalcemia of malignancy.[7-10] However, like most prescribed therapeutic agents, bisphosphonates are not 100 percent effective and are known to be associated with severe adverse events. These include renal toxicity, potentially leading to renal failure, particularly in patients with known renal impairment or risk factors for such.[9] Because of this, dose adjustments for renal impairment and continued renal monitoring during therapy are required.[9] Another rare, but serious adverse event is osteonecrosis of the jaw (ONJ), which has been shown to occur more often in patients with recent history of dental extraction.[9,11] Other adverse effects include acute-phase reactions, particularly a flu-like syndrome, bone, joint or muscular pain, and many others.[1-3, 9]

The purpose of this review is to compare the effectiveness of bisphosphonates and the novel therapeutic agent, denosumab, a human monoclonal antibody against RANKL. Research [1-3] shows denosumab is effective in reducing SREs without the need for dose adjustments for renal impairment. If denosumab proves to be more effective and has less negative side effects, it could prove to be a better option.

METHODS

Search strategy:

An exhaustive search of medical literature was performed using the following databases: Medline, CINAHL, and Web of Science. The following keyterms were used: denosumab, RANK ligand, bisphosphonates, solid tumors, and multiple myeloma.

Eligibility criteria:

Studies chosen for review include double blind, randomized, placebo controlled trials involving patients with either solid tumor or multiple myeloma who have been assigned to receive either denosumab or a bisphosphonate for the prevention of SREs associated with bone metastasis.

Validity assessment:

Validity and risk of bias of chosen studies was assessed via standard JAMA critical appraisal format, as well as GRADE criteria.

RESULTS

Comprehensive search of previously mentioned databases initially yielded 369 results. The titles and abstracts of each of these were screened and 366 were excluded because they did not meet the inclusion criteria. The full text of 3 studies whose abstracts met inclusion criteria were assessed and included in this systematic review. See Table II, Summary of Findings.

In 2011 Fizazi et al[1] conducted a double blind, randomized controlled trial of 1901 men across 342 centers in 39 countries. Participants were age ≥18 years with castration resistant prostate cancer, a solid tumor. Study participants were randomized (via computer generation by an individual outside the study) into two groups to receive either 120 mg SQ denosumab plus IV placebo every 4 weeks or 4mg IV infusion of zoledronic acid plus SQ placebo every 4 weeks (or equivalent creatinine clearance adjusted dose in patients with baseline creatinine ≤1mL/s). There were 950 participants in the denosumab group and 951 in the zoledronic acid group. Participants in each group had similar baseline characteristics, including age, race, prior occurrence of SRE, ECOG performance status, creatinine clearance, bone turnover markers, time from diagnosis of prostate cancer to randomization (months), time from diagnosis of bone metastasis to randomization (months), presence of visceral metastasis, hemoglobin concentration, PSA at randomization and Gleason score at diagnosis. [1]

The primary endpoint was time to first on-study skeletal related event, assessed for noninferiority. The secondary endpoint, which was assessed if noninferiority was found, was time to first on-study SRE for superiority as well as time to first and

subsequent SREs. The study addressed potential exploratory endpoints: overall survival, investigator-assessed overall disease progression (visceral distant metastatic disease, locoregional progression, and biochemical progression and excluding SREs), PSA concentration during the study and change in bone turnover markers from baseline. Additionally, the following safety endpoints (measured at baseline and every 4 weeks) were measured: frequency of treatment-emergent adverse events, changes in routine chemistry and hematology lab values, and presence of neutralizing anti-denosumab antibodies.[1]

Participants included in the study had histologically confirmed prostate cancer, current or prior radiographic evidence of at least one bone metastasis, documented failure of at least one hormonal therapy (using PSA level), adequate organ function, an albumin-adjusted serum calcium concentration of 2-2.9 mmol/L, and Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. Participants were excluded if they had current or prior bisphosphonate use (IV or PO) for bone metastasis (this was permitted if it was used for treatment of osteoporosis only), planned radiation or surgery to bone, life expectancy <6months, current or prior osteonecrosis or osteomyelitis of the jaw, planned invasive dental procedure during study, malignant disease other than prostate cancer within the past 3 years, or creatinine clearance < 0.5 mL/s (the study excluded these individuals because zoledronic acid, the bisphosphonate being used, is contraindicated in these patients).[1]

Two central imaging readers assessed for SREs, radiologists were masked, and a third masked reviewer adjudicated discrepancies. These surveys were done at baseline

and every 12 weeks. The results of the study indicate that denosumab is better than zoledronic acid for delaying time to onset of SREs in study participants. The hazard ratio (HR) for time to first on-study SRE was 0.82 (95% CI, 0.71 to 0.95), an 18% reduction in time to first on-study SRE with use of denosumab. The median months to first on-study SRE for denosumab and zoledronic acid were 20.7 (95% CI, 18.8 to 24.9) and 17.1 (95% CI, 15.0 to 19.4), respectively. The median number of months on study at primary analysis cut-off date was 12.2 for denosumab and 11.2 for zoledronic acid. Analysis of the secondary endpoint, time to first on-study SRE and subsequent on-study SREs, indicated a rate ratio of 0.884 and a calculated number needed to treat of 16, demonstrating that for every 16 patients treated with denosumab rather than zoledronic acid, one less will have an SRE. Results of the analysis of overall survival and disease progression between the two groups indicate there is not a statistically significant difference between the two groups. Median months of survival for denosumab and zoledronic acid were 19.4 (95% CI, 18.1 to 21.7) and 19.8 (95% CI 18.1 to 20.9), respectively. Median months to disease progression for denosumab (95% CI, 8.1 to 9.3) and zoledronic acid (95% CI, 8.2 to 9.3) was 8.4 months in each group.[1]

Adverse events were assessed at baseline and every 4 weeks. The occurrence phase reactions were greater in the zoledronic acid group. The occurrence of death was about equal between groups. ONJ was a rare event in both groups. The occurrence of hypocalcemia and CTCAE grade 3 or 4 was higher in the denosumab group. The occurrence of events “potentially associated with renal impairment” were about the same in each group, with 15% occurring in the denosumab group and 16% in the zoledronic acid group.[1] To review results of outcome measures, see Table III.

Patients were analyzed based on intention to treat. However, only 228/950 in the denosumab group and 208/951 in the zoledronic acid group were on study at the primary data analysis cut-off date. The major reasons for discontinuation were death, withdrawal of consent and disease progression, and less than 5% per group were lost to follow up.[1]

In a similar double blind, randomized control trial published in 2010 by Stopeck et al[3] denosumab was compared to zoledronic acid for analysis of the same primary (time to first on-study SRE for noninferiority) and secondary (time to first and subsequent on-study SRE for superiority) endpoints in 2,046 participants from 322 centers in Europe, North America, South America, Japan, Australia, India and South Africa. Study participants were randomized into two groups to receive either 120 mg SQ denosumab plus IV placebo every 4 weeks (n = 1,026) or 4mg IV infusion of zoledronic acid plus SQ placebo every 4 weeks (n = 1,020). The study also assessed overall survival and disease progression. Other safety end points included incidence of treatment-emergent adverse events, changes in lab values, and incidence of anti-denosumab antibodies – all were coded using the Medical Dictionary for Regulatory activities (MedDRA v 12.0 system). Oral exams (for ONJ) were performed biannually by a blinded adjudication committee of an external panel of experts.[3]

Participants included in the study were of age ≥ 18 years old with histological or cytologically confirmed breast adenocarcinoma, a solid tumor, current or prior evidence of at least one bone metastasis, adequate organ function (including albumin-adjusted serum calcium at or between 8 and 11.5 mg/dL), and Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. Exclusion criteria were outlined as

follows: creatinine clearance <30mL/min using Cockcroft-Gault formula (due to contraindication of zoledronic acid use in this population), prior IV or oral bisphosphonate treatment for bone metastases, nonhealed dental/oral surgery, and prior malignancy within 3 years before random assignment.[3]

Participants in each group had similar baseline characteristics, which include: age, ECOG status, prior SRE, having more than 2 metastatic bone lesions, prior chemotherapy and hormonal therapy, prior use of oral bisphosphonates, median time from primary cancer diagnosis to diagnosis of bone metastasis, median time from diagnosis of bone metastasis to randomization, hormone receptor status (HR/PR), HER2 status, and presence of visceral metastasis.[3]

Patients were assessed by x-ray every 12 weeks for evidence of fracture, or by other radiographic imaging at their standard care appointments, which were scheduled at baseline and every 4 weeks. At least two blinded independent radiologists and a central imaging center performed assessment for both fracture and spinal cord compression. Results of the study indicate that denosumab was noninferior to zoledronic acid, and time to first on-study SRE was delayed by 18% with denosumab compared to zoledronic acid (HR, 0.82; 95% CI, 0.71 to 0.95; $p<0.001$ noninferiority; $p = 0.01$ superiority.) The reported median time to onset of on-study SRE was 26.4 months with zoledronic acid, and was not reached during study with denosumab. The median number of months on study was 17, and the entire duration of the study, from enrollment to primary analysis, was 34 months. Time to first and subsequent SREs was delayed by 23% with denosumab (rate ratio, 0.77; 95% CI, 0.66 to 0.89; $p = 0.001$). Assessment of overall survival (HR

0.95; 95% CI, 0.81 to 1.11) and disease progression (HR 1.00; 95% CI, 0.89 to 1.11) indicates similarity between the two groups.[3]

Additional outcome measures for safety and efficacy were measured regularly. The rate of renal failure, acute phase reactions and common terminology criteria for adverse events (CTCAE) ≥ 3 occurred more commonly in the zoledronic acid group. The rate of hypocalcemia occurred more commonly with denosumab, and ONJ was a rare event in each group.[3] To review results of outcome measures, see Table III.

In the statistical analysis, patients were analyzed based on intent to treat. 45% of the zoledronic acid group and 46% of the denosumab group remained on study at primary analysis cut-off date. 17% of patients in each group died before the studies completion, and this was the most common reason for discontinuation, followed by 12% disease progression and 12% consent withdrawal; <1% of each group was lost to follow up.[3]

The final study included in this review was a double blind, double dummy, RCT by Henry et al[2] published in 2011. There were 1,779 participants from 321 centers worldwide. Participants were randomized into two groups to receive either 120 mg SQ denosumab plus IV placebo every 4 weeks (n = 86) or 4mg IV infusion of zoledronic acid plus SQ placebo every 4 weeks (n = 890). Zoledronic acid was dose adjusted for renal impairment as indicated. Randomization was performed by an independent individual, and participants were stratified by tumor type, which were non-small cell lung cancer (40%), multiple myeloma (10%) and "other" (50%). Participants in each group had similar baseline characteristics, including gender, age, ECOG status, primary tumor type,

prior SRE, median months from initial diagnosis of bone metastasis to randomization, prior "anti-neoplastic treatment", and presence of visceral metastases.[2]

The same primary and secondary endpoints as the prior two studies were assessed in this trial. Exploratory endpoints include bone turnover markers measured at baseline and week 13, overall survival, and overall disease progression.[2]

Inclusion criteria for participants is outlined as follows: age ≥ 18 years old with histologically or cytologically confirmed solid tumors (except breast or prostate) or myeloma and radiographic evidence of at least 1 bone metastasis or osteolytic lesion, creatinine clearance ≥30 mL/min, and ECOG performance status ≤ 2. Patients were excluded if they had prior treatment with IV bisphosphonates, planned radiation or surgery to bone, or unhealed dental/oral surgery.[2]

Blinded, external radiologists at a central imaging center performed assessment of outcomes at baseline, and every 12 weeks or at routine appointments as indicated. Results of the study indicate that denosumab is noninferior to zoledronic acid in delaying time to first on-study SRE (HR, 0.84; 95% CI, 0.71-0.98). This represents a 16% reduction in SREs with use of denosumab rather than zoledronic acid. The total length of the study was 34 months, however, the reported median time to first on-study SRE was 20.6 months in the denosumab group, and 16.3 months in the zoledronic acid group. "Median time (quartile [Q]1, Q3) on study was approximately 7 months (Q1, 3; Q3, 14)."[2] Assessment for time to first and subsequent SREs and superiority was not statistically significant (rate ratio 0.90, 95% CI, 0.77 to 1.04). These results indicate that there is 10% reduction in time to first and multiple SREs, with a NNT of 21. Overall survival (HR

0.95, 95% CI, 0.83 to 1.08) and disease progression (HR 1.00; 95% CI, 089-1.12) were similar between groups.[2]

Adverse events were assessed at regular intervals by an external data monitoring committee. The incidence of renal failure, acute phase reactions, and CTCAE grade ≥ 3 was greater in the zoledronic acid group. The incidence of hypocalcemia was greater in the denosumab group, and the incidence of ONJ was rare in both groups.[2] To review results of outcome measures, see Table III.

In the statistical analysis, patients were analyzed based on intent to treat. Only 20% of participants remained on-study at primary analysis cut-off date (zoledronic acid group, n=178; denosumab group, n=180). The top 3 reasons for discontinuation were death (35%), disease progression (13%) and consent withdrawn (15%). Loss to follow up in the denosumab and zoledronic acid group was 2.5% and 1.8% respectively.[2]

DISCUSSION

Summary of main findings (Table II):

This review of studies [1-3] illustrates the increased benefit of denosumab compared to the standard treatment, bisphosphonates, in preventing or delaying time to onset of SREs in patients with solid tumor cancer and multiple myeloma. While these results are positive, it should be noted that the assessment of overall survival and disease progression was similar between groups in each of the trials reviewed. Since overall survival and disease progression are similar with both agents, the decision regarding which therapy to use should also include review of adverse events associated with each agent individually, as well as ease of administration.

An overview of selected adverse events can be found in Table III. The adverse events that showed the greatest discrepancy between treatment arms were the incidence of renal failure, hypocalcemia and acute phase reactions. The rate of renal failure was higher in those receiving zoledronic acid. Because denosumab is not contraindicated in patients with renal impairment it is a potential option for those patients. The rate of ONJ was about the same between groups, but was a rare event. Additionally, the occurrence of acute phase reactions, including flu-like syndrome, were much higher in those taking zoledronic acid. Hypocalcemia was more common in the denosumab group, but is easily managed by careful monitoring and supplementation as indicated. With regard to ease of administration, denosumab is easier to administer with a subcutaneous injection rather than an IV infusion, which is required for zoledronic acid administration.

Overall completeness and applicability of evidence

A possible limitation consistent across studies is the difference between the number of participants at onset of each trial and at studies completion. Although, loss to follow up was minimal, the rate of death was quite high and cause of death, whether due to therapy or disease progression, was not clearly stratified in each of the studies. One counter measure to this limitation is that each study was analyzed by the intention to treat principle, and each study maintained a sufficient number of participants to account for the significance of the results in spite of the high rate of deaths in each study.

One notable limitation of the study authored by Henry et al [2] is that participants are not completely stratified by tumor type, but rather are characterized by the diagnosis of non-small cell lung cancer (40% of patients in each randomized group), multiple myeloma (10% of patients per randomized group), or “other” (50% of patients per

randomized group). The “other” category consists of participants with solid tumors, but because their tumor type is unknown, and they comprise at least half of the entire study population it may be difficult to confer particular relevance to these results in individual incidents.

An additional limitation of these studies is that participants with creatinine clearance less than 30 mL/minute were excluded from each of the trials based on zoledronic acid protocol. In studies comparing denosumab to placebo alone, these participants can be included because renal impairment is not a contraindication. However, in studies, such as those in this review, which are a head to head comparison of denosumab and zoledronic acid, participants with this level of renal impairment cannot be assessed.

A further possible limitation of applicability, based on these studies, is the use of denosumab is patients who have used bisphosphonates in the past. Prior bisphosphonate use by potential participants was part of the exclusion criteria in each of the trials. Another potential avenue of research includes use of denosumab in patients who have previously used bisphosphonates, with or without success, to determine if denosumab would in fact be more efficacious and potentially increase quality of life for these people.

Quality of evidence

Each of the trials included in this review are randomized controlled trials that have been evaluated for quality using the GRADE criteria. Each study received a rating of “high”. The characteristics of reviewed studies can be found in Table I.

Potential biases in the review process

The funding source for each trial may have opened the window to potential for causing bias. Amgen funded and performed data collection and analysis of the Fizazi et al trial.[1] Authors of the study, some of whom were employed by Amgen, interpreted the data. A medical writer provided by Amgen assisted the authors in drafting and reviewing the study. The study authored by Stopeck et al was "supported" by Amgen and Daiichi Sankyo. Some of the authors of the study did claim a financial interest in the subject and these individuals were clearly listed at the conclusion of the article. The authors of the study contributed to conception and design, provision of study material or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript.[3] Research for the study authored by Henry et al was funded by several individuals (one of which is an author) from both Amgen and Novartis.[2] The risk of bias was potentially reduced by the extensive degree of blinding in various aspects of each trial, including randomization, assessment of outcomes, and the double dummy design.

CONCLUSION

The systematic review process has demonstrated that, based on findings in each of these high quality studies, denosumab is a better agent for delaying onset to SREs in patients with both solid tumors and multiple myeloma. Denosumab also has other advantages to be considered in practice. Denosumab does not require dose adjustment for renal impairment, nor is renal monitoring necessary during therapy. Also, it is less likely

to cause acute phase reactions, which may potentially reduce some burden of therapy for the patient. Denosumab did, however, demonstrate a higher rate of hypocalcemia, which implies that therapy requires close monitoring and supplementation as indicated. The benefits of improved effectiveness of therapy, ease of administration, and decrease in rate of adverse events may potentially be extended to another patient important outcome of an increase in quality of life.

Research of supportive therapy for prevention of SREs in solid tumor and multiple myeloma patients has shown progress with the novel RANKL therapy. However, other physiological pathways, or improvements in the pharmacotherapeutics of current therapy should be addressed and considered in future research for the purposes of discovering both more effective, and less toxic therapy.

In addition, further research of an increased duration is necessary to assess both the long-term effectiveness and risk of denosumab. Obviously, such research has not been possible due to the youth of denosumab. However, it should commence as soon as possible and be continued for a significant amount of time.

Reference:

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Table I. Characteristics of Reviewed Studies

Study	No of participants in Denosumab group	No of participants in ZA group	Age	Randomization	Allocation Concealment	Description of loss to follow up	Blinding of outcome assessors	Intention to treat analysis	Approx. median time on study (months)
Fizazi, K., et al [1]									
	950	951	≥18 yrs	Yes	Yes	Yes	Yes	Yes	D,12.2 Z, 11.2
Stopeck, A. et al. [2]									
	1,026	1,020	≥18 yrs	Yes	Yes	Yes	Yes	Yes	17
Henry, D., et al. [3]									
	886	890	≥18 yrs	Yes	Yes	Yes	Yes	Yes	7

D: Denosumab; ZA: Zoledronic Acid

Table II. Summary of Findings

	Median time to first on-study SRE (months)	Hazard Ratio	Time to subsequent on-study SREs	Survival	Disease progression	Quality
Importance of Outcome	Critical		Critical	Critical	Critical	
Fizazi, K., et al [1]	D: 20.7 ZA: 17.1	0.82	RR = 0.884	D: 19.4 months ZA: 19.8 months	Median mo. D: 8.4 ZA: 8.4	HIGH
Stopeck, A. et al. [3]	D: not reached ZA: 26.4	0.82	RR = 0.77	HR 0.95	HR 1.00	HIGH
Henry, D., et al. [2]	D: 20.6 ZA: 16.3	0.84	RR = 0.90	HR 0.95	HR 1.00	HIGH

D: Denosumab; ZA: Zoledronic Acid; RR: Rate Ratio; HR: Hazard Ratio

Table III. Summary of reported Adverse Events (Abbreviated)

	ONJ		**Renal failure**		**Hypocalcemia**		**Acute phase reactions (first 3 days)**		**CTCAE grade ≥ 3 (grade 5 listed separately in Fizazi)**	
	Den	ZA	Den	ZA	Den	ZA	Den	ZA	Den	ZA
Fizazi, K. [1]	2.0%	1.0%	NR	NR	13.0%	6.0%	8%	18%	72% Grade 5 (death): 30%	66% Grade 5: 29%
Stopeck, A. [3]	2.0%	1.4%	0.2%	2.5%	5.5%	3.4%	10.4%	27.3%	59.7%	62.7%
Henry, D., et al [2]	1.1%	1.3%	2.3%	2.8%	10.8%	5.8%	6.9%	14.5%	77%	80%

Den: Denosumab; ZA: Zoledronic Acid; ONJ: osteonecrosis of the jaw; CTCAE: Common Terminology Criteria for Adverse Events; NR: Not reported